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TITLE: Optical Transillumination Spectroscopy of Breast Tissue
to Determine the Cancer Risk in Pre- and Post-Menopausal
Women

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13. Abstract (Maximum 200 Words) (abstract should contain no proprietary or confidential information) The objective of this study is to demonstrate a correlation between non-invasive optical transillumination spectroscopy and parenchymal density pattern, which are known to provide the highest odds ratio for the risk of developing breast cancer. The study includes pre- and post-menopausal women. Initial results indicate that optical transillumination spectroscopy can differentiate between high and low parenchymal density with sensitivity and specificity > 90 for the study group (n= 225), after the introduction of stratification for the position on the breast. Additional analysis models the percent dense tissue area from the measured transillumination spectrum. A separate study investigates the influence of the menstrual cycle upon the transillumination spectra and no significant effects are noted.				
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Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	6
Reportable Outcomes.....	6
Conclusions.....	7
References.....	7
Appendices.....	8

INTRODUCTION:

This study combined two previously published observations, relating to the ability of quantitative optical transillumination spectra to quantify a woman's probability of having breast cancer and the predictive value parenchymal density pattern have to predict a woman's risk to develop breast cancer. The structures providing x-ray attenuation will also affect the optical transillumination spectrum. Hence, this cross-sectional study is aimed at identifying and quantifying correlations between parenchymal density pattern as observed on standard x-ray mammography and optical transillumination spectra. Patients who had their x-ray mammograms taken during the preceding 12 month are recruited into the study (see Table 1 for recruitment to date) with some of them partaking in either of 2 sub-studies, 4 repeat measurement over the menstrual cycle, or additional frequency domain measurements.

The obtained transillumination spectra are corrected for the instrument response, normalized for the tissue thickness and either classified according to the groups indicated in Table 1 or the percent dense area is determined using a software assisted thresholding. Numerical methods such as Principle Component Analysis (PCA) or Principle Component Regression (PCR) are used to establish correlation to the parenchymal density pattern classes or percent density respectively.

Table 1: Total intended recruitment and success to date.

		Study 1: Single Visit		Study 1a: Frequency domain		Study 2: Menstrual cycle	
		Proposed	August 25 th	Proposed	July 20 th	Proposed	July 20 th
Pre-menopause	Low	50	22	10	0	20	12
	Med.	50	44	10	0	20	23
	High	50	18	10	0	20	13
Post-menopause	Low	50	57	10	0	20	0 *
	Med.	50	49	10	0	20	0 *
	High	50	13	10	0	20	0 *

* No suitable volunteers have been identified to date.

BODY

The progress report below is structured according to the three tasks described in the original submission.

- Task 1. Instrument improvements:

The currently used 2D back-thin CCD array by Photometrix has proven very reliable and with the limited dark noise due to liquid nitrogen cooling, good quality spectra through up to 8 cm of breast tissue are obtained. Various attempts to use direct frequency domain spectroscopy to determine the phase shift were unsuccessful and a heterodyne system operating at 100 MHz was constructed and tested the first volunteers are to be measured now in September 2002. To accomplish recruiting fast we have previously asked volunteers if they are willing to come for an extra visit for these measurements and the available cohort will enable us to complete Study 1a within 40 days

- Task 2. Correlation of optical transillumination spectroscopy and parenchymal tissue density pattern:

Table 1 above provides the recruitment record to date. Since seeing the first patient March 21 2001, we continue to recruit at a steady pace of 15 volunteers per week. Recruiting is performed now through the Marvel Koffler Breast Imaging Centre at Mount Sinai Hospital and the Breast imaging centre at the Princess Margaret Hospital in Toronto ON has been added as an additional recruitment site (). The only subgroup we are experiencing problems is with postmenopausal women on HRT who are still experiencing a (mini) period.

Multi variant analysis showed that while time during menstrual cycle is not a statistically significant parameter position on the breast is statistically significant.

See also Figure 1 showing the cluster analysis with PC1 and PC2 as input for a group of pre-menopausal women. Hence, it may be that transillumination spectroscopy is not sensitive to the tissue changes related to the menstrual cycle and for cycles in women on HRT. (Note: this does NOT reflect on the possible of women on HRT have higher breast densities. An analysis to this effect is currently underway). The fact that no menstrual dependence is seen in the cluster plots needs to be repeated for an analysis using more parameters, e.g. 3D, see below and additionally a power analysis is to be completed to exclude menstrual changes from consideration in spectra interpretation during further development of the transillumination technique.

The correlation between mammographic tissue densities and transillumination spectra are established using nominal (classifications) and interval (% area of dense tissue) data. shows a 3D plot of PC1, PC2 and PC4 delineating patient classified with high versus those classified with low breast tissue density in the centre position. Table 2 gives the specificity and sensitivity to identify women with high breast density form those with low density without stratification and stratified for the position on the breast.

Table 2. Sensitivity and specificity for the training data set and validation data set using all measurement positions and only individual measurement positions.

Position and Component Scores Used	Training Set		Validation Set	
	Sensitivity	Specificity	Sensitivity	Specificity
All positions (Components 1, 2 and 3)	76.9%	88.3%	75.0%	96.7%
Centre (Components 1, 3 and 4)	95.0%	87.0%	92.9%	90.0%
Medial (Components 1, 3 and 4)	82.5%	56.5%	85.7%	70.0%
Distal (Components 1, 2 and 4)	90.0%	91.3%	100.0%	100.0%
Lateral (Components 1, 2 and 3)	82.5%	96.7%	78.6%	100.0%

We noticed additionally that the principle components are dependent on age and body mass index and current effort are being undertaken to correct these two accordingly, assuming that the specificity and sensitivity will improve.

Figure 3 shows a correlation plot between the transillumination spectra based % dense breast and the mammographic determined % dense breast values including the confidence intervals. (Note:

PLS and PCR require a training set, usually comprised of 75% of the data and a validation set comprised of 25% of the data and hence 2 confidence intervals for the data is given). Correlation values for non-stratified data are about 0.8 which is acceptable as the correlation between the different individuals (one expert and 3 trained readers) quantifying the % density from the mammograms using a computer assisted program is also only around 0.8. Current efforts are centered on improving the training of 3 readers to improve the reliability of our standard measure.

- Task 3. Derivation of tissue chromophore concentrations and light scattering properties of the breast tissue.

Most of the studies related to Task 3 are scheduled for the latter years and require the implementation of the frequency domain measurements which are a prerequisite for the PLS analysis and the chromophores concentration determination. While there was a delay, we are poised to obtain this data within a very short period of time as indicated above.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- Optical transillumination spectroscopy appears to be able to identify women with high parenchymal density pattern with very good sensitivity and specificity if analysis is stratified according to the position of the breast where the measurement was taken.
- Sensitivity and specificity of identifying women with high versus low breast tissue densities of approximately 0.9 are obtainable, equally in pre and post-menopausal women.
- Using interval data analysis showed that correlation between mammographically determined and transillumination determined densities is high at 0.8.
- Approximately 220 out of 300 targeted volunteers were recruited to date.

REPORTABLE OUTCOMES:

List of conference presentations:

SPIE Photonics West January 2002

Optical Transillumination Spectroscopy of Breast Tissue for Assessment of Breast Cancer Risk
Michelle K. Simick, Brian C. Wilson, Lothar Lilge

To enable early cancer detection, screening of the population at risk for cancer is essential. Currently, tissue density patterns seen on standard x-ray mammography are used to assess breast cancer risk in the clinic. These patterns reflect the ratio of glandular tissue to adipose tissue within the breast. An increased ratio of dense glandular tissue indicates higher risk with an odds ratio of approximately 6.

Many groups have also demonstrated that physiology of the breast tissue can be established based on the near-infrared optical transillumination spectra. Similarly the adipose and glandular tissue ratio responsible for the density pattern can also result in unique optical transillumination spectra. In this study we are attempting to consider patients that have had mammograms and examine them optically, to correlate density and therefore risk estimation between optical and x-ray measurements.

Invited presentation at the Wellman Laboratories of Photomedicine, Massachusetts General Hospital, November 2001

Transillumination Spectroscopy for Breast Cancer Risk Assessment

Lothar Lilge, Michelle Simick

SPIE Opto-Canada. June 2002

Transillumination Spectroscopy for Breast Cancer Risk Assessment

Michelle Simick, Lothar Lilge

Abstract

One way to assess an individual's breast cancer risk is to use tissue densities seen on standard x-ray mammography. Large areas of dense, glandular tissue indicate a higher breast cancer risk category with an odds ratio of up to 6.

Near-infrared optical transillumination spectroscopy has been shown previously to be helpful in investigating physiological and anatomical properties of the breast tissue. The areas of adipose and glandular tissues are responsible for the mammographic density patterns and have been shown to result in unique optical transillumination spectra.

In this study, subjects with previous mammograms underwent examination of their breast tissue by optical transillumination spectroscopy. Correlation between optical transillumination spectroscopy and mammographic density pattern is established using Principal Component Analysis, Linear Discriminant Analysis, Principal Component Regression and Partial Least Squares Analysis. Results indicate that x-ray dense tissue can be identified accuracy above 85% when compared to low density tissue.

Ms. Michelle Simick will defend her M.Sc. in the Department of Medical Biophysics on September 4th 2002. Topic of her Thesis is "Near Infrared Transillumination Spectroscopy of Breast Tissue for Correlation with Mammographic Density"

CONCLUSIONS:

The current work provides initial support to the hypothesis that optical transillumination spectroscopy can provide information about parenchymal density pattern in the female breast. At this point I do not see reasons to alter the previously indicated research course.

REFERENCES:

No references applicable in this report, however, a total of 2 papers to be submitted to peer reviewed journals are being prepared currently and will be finished immediately after the Thesis proceedings for Ms. Michelle Simick are concluded.

APPENDICES:

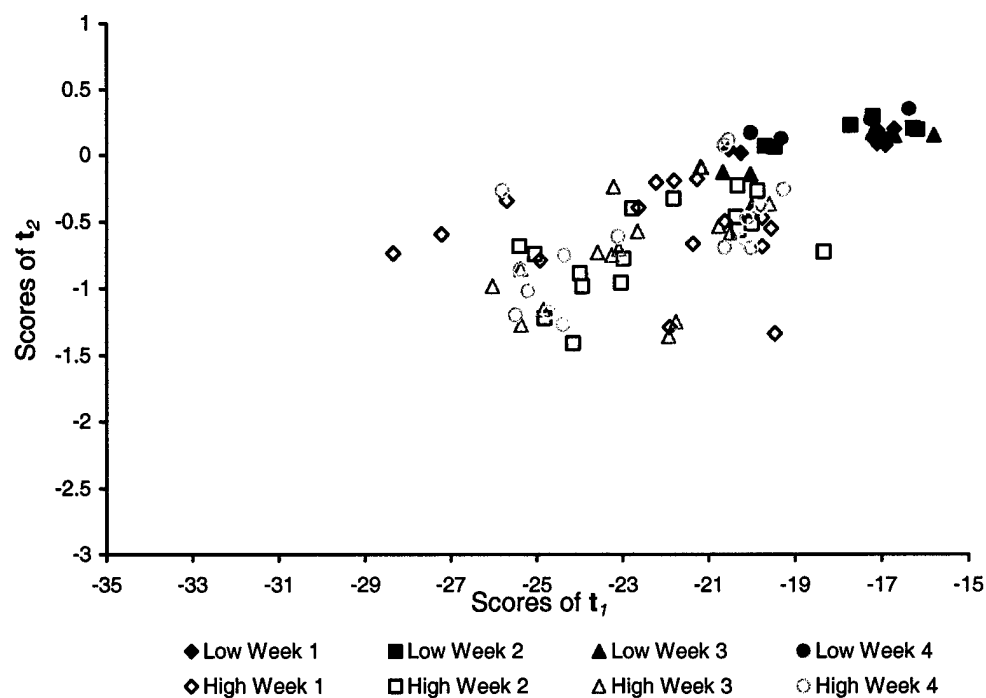


Figure 1 Cluster analysis with PC1 and PC2 as input for a group of pre-menopausal women, showing non significant or reproducible changes in PC1 or PC2 as function of menstrual cycle.

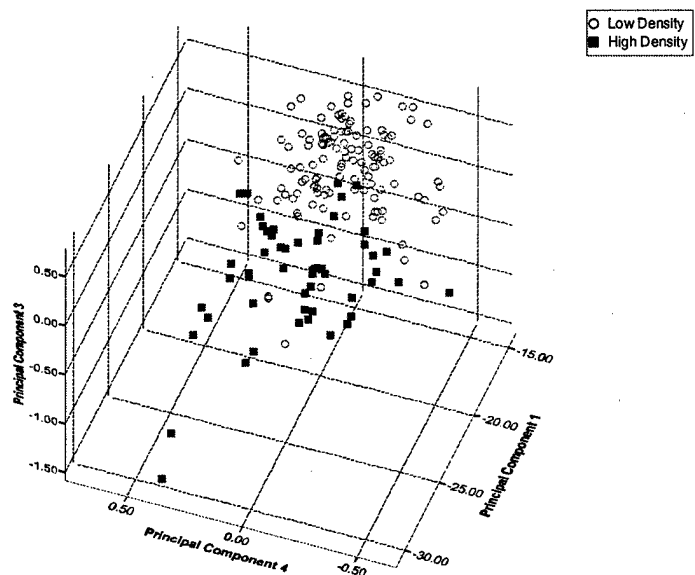
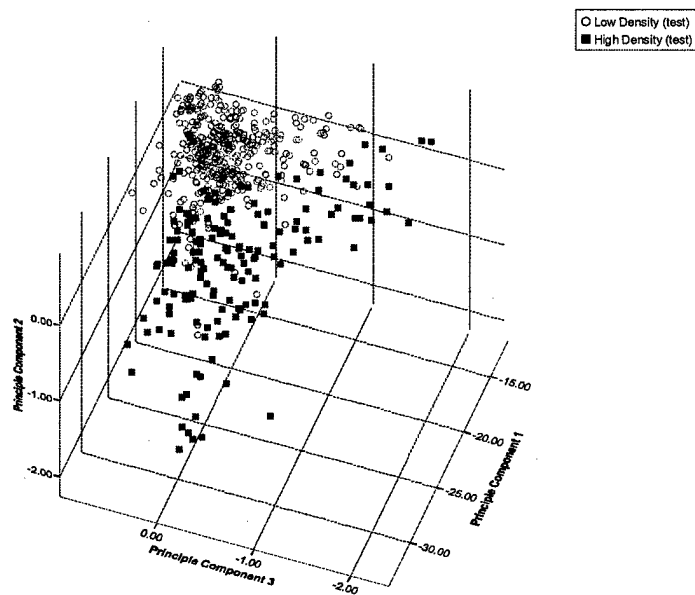


Figure 2 3D plot of PC1, PC2 and PC4 delineating patient classified with high versus low breast tissue density top) for all 4 positions and bottom) only for the centre. Similar plot are available for the other 3 measurement positions (data not shown)

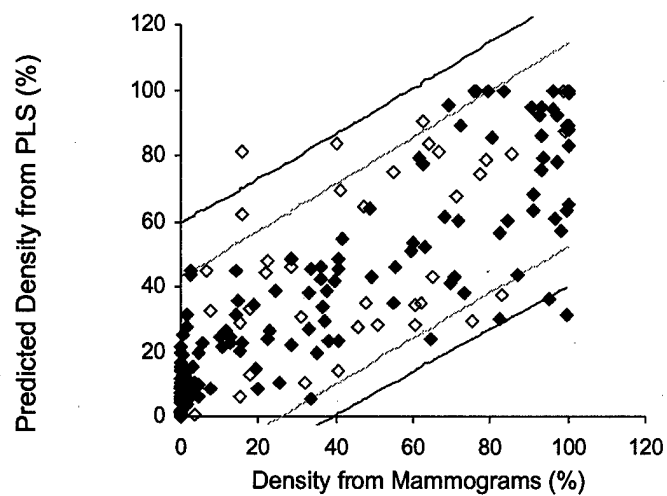


Figure 3 Correlation plot showing the transillumination spectra based determined % dense breast versus the mammographic determined % dense breast values including the confidence intervals for the training (solid symbols) and validation (open symbols) set .